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Derivation and external validation of the SHIeLD score for predicting outcome in normotensive pulmonary embolism☆

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A B S T R A C T

Background: Identifying patients with normotensive pulmonary embolism (PE) who may benefit from thrombolysis remains challenging. We sought to develop and validate a score to predict 30-days PE-related mortality and/or rescue thrombolysis.

Methods: We retrospectively assessed 554 patients with normotensive PE. Independent predictors of the studied endpoint were identified from variables available at admission in the emergency department and were used to create a score. The model was validated in 308 patients from a separate hospital.

Results: A total of 64 patients died or needed rescue thrombolysis (44 in the derivation cohort). Four independent prognostic factors were identified: ***S***hock index ≥ 1.0 (OR 3.33; 95% CI 1.40–7.93; P = 0.006), ***H***ypoxaem***I***a by the PaO_2/FiO_2 ratio (OR 0.92 per 10 units; 95% CI 0.88–0.97; P < 0.001), ***L***actate (OR 1.38 per mmol/L; 95% CI 1.09–1.75; P = 0.008) and cardiovascular ***D***ysfunction (OR 5.67; 95% CI 2.60–12.33; P < 0.001) – SHIeLD score. In the development cohort, event rates for each risk tercile were 0.0%, 2.2%, and 21.6%. In the validation cohort, corresponding rates were 0.0%, 1.9%, and 14.3%. The C-statistic was 0.90 (95% CI 0.86–0.94, P < 0.001) in the derivation cohort and 0.82 (95% CI 0.75–0.89, P < 0.001) in the validation cohort. Decision curve analysis showed that the SHIeLD score is able to accurately identify more true positive cases than the European Society of Cardiology decision criteria.

Conclusions: A risk score to predict 30-days PE-related mortality and/or rescue thrombolysis in patients with normotensive PE was developed and validated. This score may assist physicians in selecting patients for closer monitoring or aggressive treatment strategy.

1. Introduction

Although patients with normotensive pulmonary embolism (PE) are a prognostically heterogeneous population, the best way to identify those who might benefit from an early aggressive treatment strategy is a matter of ongoing debate. The European Society of Cardiology (ESC) guidelines recommend risk stratification of normotensive PE patients using a set of clinical variables gathered in the Pulmonary Embolism Severity Index (PESI) score, and imaging or blood markers of right ventricular (RV) dysfunction [1]. This allows PE to be categorized into low, intermediate-low and intermediate-high risk. While this risk stratification tool is a step-up in the prognostic assessment, there is still a subset of normotensive PE patients at a higher risk of hemodynamic decompensation and death who need to be adequately identified [2,3]. Several scores have been developed to address this problem [4,5]. However, most of them use imaging data (for example echocardiography and lower limb ultrasound) that may not be readily available in a busy emergency department.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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The pathophysiology of PE is related to cardiovascular and pulmonary gas exchange abnormalities. The resulting hypoxemia associated with the increase in RV pressure initiates a cascade of RV injury and dysfunction that results in hypotension and ultimately death [1]. Somewhere along this cascade, a status of compensated shock with cellular hypoxia and major organ injury may develop, without (and prior to) overt hypotension. We hypothesized that cardiovascular and pulmonary dysfunction and their systemic consequences could be combined in a multi-marker score to be applied at the time of diagnosis to predict PE-related death and/or rescue thrombolysis at 30-days in normotensive PE patients. A derivation cohort was used for model development which was subsequently validated in an external cohort.

2. Methods

2.1. Study population

In this retrospective study, we used the International Statistical Classification of Diseases and Related Health Problems (9th Revision) to identify consecutive patients aged ≥18 years old presented at the emergency department (ED) with acute symptomatic PE.

According to the 2014 ESC guidelines, risk stratification should initially be based on the patient's clinical status at presentation that delineates diagnostic and therapeutic strategies [1]. Haemodynamically unstable patients with shock or hypotension (defined as systolic blood pressure < 90 mm Hg or a systolic pressure drop by ≥40 mm Hg for >15 min) should be regarded as high-risk patients were thrombolysis is warranted [1]. All other patients are not-high-risk where further risk stratification is conducted by clinical characteristics (gathered in the PESI score) and the presence of myocardial injury markers [troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP)] and imaging signs of RV dysfunction. Amongst non-high-risk patients, close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of reperfusion therapies. As such, 'rescue thrombolysis' refers only to thrombolysis that was administered in a patient that presented normotensive (not-high-risk) but in whom clinical deterioration developed with arterial hypotension or shock.

Exclusion criteria comprised: 1) high-risk PE; 2) physician's decision to perform thrombolysis in non-high-risk patients despite absence of haemodynamic decompensation; 3) sub-segmental PE; 4) loss to follow-up (unknown outcome at 30 days).

The study protocol was reviewed and approved by the ethics' committee of all participating centres, which waived the need for informed consent.

2.2. Derivation and external validation cohorts

The derivation cohort consisted of 554 normotensive PE patients identified at the ED of *Centro Hospitalar de Lisboa Ocidental* in Lisbon (tertiary academic centre), Portugal, between September 2009 and December 2017. The external validation cohort consisted of 308 normotensive PE patients enrolled at the ED of the *Hospital Prof. Dr. Fernando Fonseca* in Amadora (secondary non-academic centre), Portugal, between October 2013 and December 2016.

2.3. Physical signs, laboratory and multi-detector computed tomography (MDCT) measurements

Physical signs, blood samples and arterial blood gas were collected on admission in the ED. Shock index refers to the ratio between heart rate and systolic blood pressure. In the derivation cohort a conventional Troponin I test (99th percentile: 0.040 μg/mL) was used until February/2016, when it was switched to a high-sensitivity Troponin T test (99th percentile: 14 ng/L). In the validation cohort only a conventional Troponin T test (99th percentile: 0.050 μg/mL) was available between 2013 and 2016. To account for the use of different biochemical assays, we created a ratio between the measured troponin value and the respective 99th percentile cut-off value (measured troponin/reference value). For example, a measured troponin/reference value ratio of 4 would mean that the measured troponin was 4 times higher than the 99th percentile cut-off value. For NT-proBNP, the cut-off value was 600 pg/mL [6]. Acute kidney injury was defined according to KDIGO recommendation [7]. The degree of hypoxaemia was assessed by the ratio between the arterial partial pressure of oxygen and the fraction of inspired oxygen (PaO_2/FiO_2).

Acute PE was defined as a new segmental or more proximal pulmonary artery filling defect found at MDCT angiography. RV dysfunction was considered present by a short-axis RV/LV diameter ratio ≥ 1.0 at MDCT [8,9]. In line with current guidelines, cardiovascular dysfunction was defined as the cumulative presence of elevated troponin, elevated NT-proBNP and RV/LV ratio ≥ 1.0 [1].

2.4. Study endpoints

The primary study endpoint was a composite of PE-related mortality and/or rescue thrombolysis at 30-days. The cause of death was adjudicated by the local investigators, who were blinded to the score results, after careful review of patients' medical records. Death was related to PE if: 1) it followed a clinically severe, objectively diagnosed PE; 2) it was sudden or unexpected and could not be explained by a more compelling alternative diagnosis.

The secondary study endpoints were: 1) composite of all-cause mortality and/or rescue thrombolysis; 2) all-cause mortality and; 3) PE-related mortality at 30-days.

2.5. Statistical methods

Continuous variables with normal distribution are presented as mean ± standard deviation, whereas those with non-normal distribution are presented as median and interquartile range. Categorical variables are presented as frequency and percentage. Baseline characteristics were compared using Pearson's chi-square for categorical variables and Student *t*-test or Mann-Whitney *U* test for continuous variables.

Overall, the rate of missing data was 1.8% ($n = 571$ entries). To account for this, we performed multiple imputation ($n = 26$) using chained equations [10]. All statistical analyses performed thereafter were pooled. A sensitivity analysis (excluding patients with missing variables) was performed to assess any potential bias introduced by the imputation model. Online Supplementary material provides further details on this procedure.

Univariate logistic regression analysis was applied in the derivation cohort to relate a broad range of admission parameters to the study endpoint. After correction for multicollinearity, variables with a P value < 0.05 were selected for multivariate analysis using a logistic regression model (additional information is available in the online Supplementary material). Patients were divided into terciles (lowest, intermediate and highest risk) according to the final model score. Calibration was assessed by calibration plots, calibration-in-the-large (α) and calibration slope (β). The discriminative ability was quantified using ROC curve analysis. Internal validation was performed with bootstrapping (1000 samples). Kaplan-Meier survival curves were plotted for each risk tercile. The log-rank test was used to assess the significance of time to endpoint differences between the risk strata.

The clinical utility of the final model was studied with the decision curve analysis [11]. Decision curves plot the net benefit of the risk predicted by any model across different risk thresholds. The net benefit is the total true-positive classifications minus the total false-positive classifications, weighted by the odds of the risk threshold. In summary, the net benefit is interpreted as the number of true-positive classifications adjusted for the detrimental effect of false-positive classifications. To put the net benefit in context, we compared the net benefit of our model with that of the ESC, PESI and Bova scores [4].

The analysis followed the framework for derivation and validation of prediction models proposed by others [12]. The reporting followed the TRIPOD statement [13]. All tests were 2-sided and statistical significance was accepted if P value < 0.05. Analyses were performed using SPSS® 25.0 and Stata® 13.0.

3. Results

3.1. Baseline characteristics

A total of 980 patients with symptomatic, normotensive, acute PE diagnosed by MDCT angiography were admitted in the emergency departments of both institutions. Amongst these, 118 patients were excluded (47 patients with high-risk PE at admission; 18 patients whom physicians decided to perform thrombolysis despite hemodynamic stability; 42 patients with sub-segmental PE; and 11 patients were lost to follow-up), leading to a final study sample of 554 patients in the derivation cohort and 308 patients in the validation cohort.

Baseline patient characteristics of both cohorts are presented in Table 1. The incidence of the study endpoint was 7.9% in the derivation cohort (28 PE-related deaths and 16 rescue thrombolyses) and 6.5% in the external validation cohort (13 PE-related deaths and 7 rescue thrombolyses). The median time to PE-related death was 6 days in the derivation cohort and 4 days in the validation cohort, while the median time to rescue thrombolysis was 1 day in both cohorts.

3.2. Model derivation for PE-related mortality and/or thrombolysis at 30-days

The final model was derived from the derivation cohort of normotensive PE patients ($n = 554$; 44 events). Table 2 shows the results of univariate analysis. After correction for multicollinearity, the multivariate analysis (see Supplementary material online) identified CV dysfunction (adjusted OR 5.67; 95% CI 2.60–12.33; P < 0.001), shock index ≥ 1.0 (adjusted OR 3.33; 95% CI 1.40–7.93; P = 0.006), lactate level (adjusted OR 1.38 per mmol/L; 95% CI 1.09–1.75; P = 0.008) and PaO_2/FiO_2 ratio (adjusted OR 0.92 per 10 units; 95% CI 0.88–0.97; P < 0.001) as independent predictors of events.

Table 1
Baseline characteristics in the derivation and validation cohorts.

	Derivation cohort *n* = 554	Validation cohort *n* = 308	P value
Clinical characteristics			
Age	76 (65–83)	71 (56–80)	<**0.001**
Men	218 (39.4%)	120 (39%)	0.911
Active cancer	116 (20.9%)	90 (29.2%)	**0.006**
Heart failure history	136 (24.5%)	48 (15.6%)	**0.002**
Chronic lung disease	111 (20.0%)	57 (18.5%)	0.587
Clinical symptoms and signs at admission			
Dyspnoea	367 (66.2%)	213 (69.2%)	0.383
Chest pain	201 (36.3%)	107 (34.7%)	0.651
Syncope	60 (10.8%)	39 (12.7%)	0.419
SBP (mm Hg)	130 (116–148)	127 (112–144)	0.094
Heart rate (bpm)	90 (80–107)	87 (74–102)	<**0.001**
Shock index (HR/SBP)	0.70 (0.58–0.84)	0.68 (0.56–0.82)	0.123
Shock index ≥ 1.0	53 (9.6%)	29 (9.4%)	0.942
Respiratory rate (cpm)	20 (16–30)	19 (16–21)	<**0.001**
Temperature (°C)	36.2 (36–36.7)	36.3 (36–36.7)	0.087
SpO_2 (%)	94 (90–97)	96 (93–98)	<**0.001**
Altered mental status	72 (13%)	83 (26.9%)	<**0.001**
Laboratory data on admission			
Haemoglobin (g/dL)	12.7 (11.3–14.0)	12.7 (11.3–13.9)	0.832
ALT (U/l)	26 (20–41)	34 (21–60)	<**0.001**
Troponin/reference[a]	1.17 (0.50–4.77)	0.95 (0.24–4.80)	<**0.001**
Elevated troponin	284 (51.3%)	147 (47.7%)	0.296
NT-proBNP (pg/mL)	1102 (275–4516)	1216 (307–4575)	0.857
Elevated NT-proBNP	337 (60.8%)	195 (63.3%)	0.416
Admission Cr (mg/dL)	0.96 (0.75–1.25)	1.07 (0.88–1.34)	<**0.001**
Baseline Cr (mg/dL)	0.80 (0.70–1.00)	0.81 (0.71–1.00)	0.341
AKI class			<**0.001**
None	470 (84.8%)	229 (74.4%)	
I	51 (9.2%)	50 (16.2%)	
II	25 (4.5%)	20 (6.5%)	
III	8 (1.4%)	9 (2.9%)	
MDCT angiography			
Central PE	247 (44.6%)	123 (39.9%)	0.145
RV/LV ratio	0.95 (0.82–1.13)	0.93 (0.82–1.11)	0.537
RV/LV ratio ≥ 1.0	227 (41%)	121 (39.3%)	0.628
CV dysfunction[b]	132 (23.8%)	68 (22.1%)	0.636
Arterial blood gas on admission			
FiO_2	0.21 (0.21–0.28)	0.21 (0.21–0.32)	<**0.001**
pH	7.44 (7.41–7.47)	7.45 (7.42–7.49)	**0.011**
$PaCO_2$ (mm Hg)	33 (30–37)	34 (30–40)	**0.021**
PaO_2 (mm Hg)	70 (59–85)	68 (58–81)	0.076
Lactate (mmol/L)	1.30 (0.99–1.91)	1.33 (1.00–1.98)	0.525
PaO_2/FiO_2	305 (249–364)	274 (191–345)	<**0.001**

Abbreviations: ALT = alanine aminotransferase; AKI = acute kidney injury; Cr = creatinine; CV = cardiovascular; FiO_2 = fraction of inspired oxygen; LV = left ventricle; MDCT = multi-detector computed tomography; NT-proBNP = N-terminal pro b-type natriuretic peptide; $PaCO_2$ and PaO_2 = arterial partial pressure of carbon dioxide and oxygen; PE = pulmonary embolism; RV = right ventricle; SpO_2 = oxygen saturation; SBP = systolic blood pressure.
All continuous values are presented as median (interquartile range). Bold values denote statistical significance.
[a] Since different troponin assays were used, a ratio between measured troponin and reference values was created for statistical analysis. For example, a measured troponin/reference value ratio of 4 would mean that the measured troponin was 4 times higher than the 99th percentile cut-off value.
[b] CV dysfunction was defined as elevated troponin, elevated NT-proBNP and RV/LV ratio ≥ 1.0.

Table 2
Univariate analysis in the derivation cohort.

	No events *n* = 510	Events *n* = 44	P value
Clinical characteristics			
Age	76 (66–83)	75 (63–84)	0.636
Men	197 (38.6%)	21 (47.7%)	0.238
Active cancer	104 (20.4%)	12 (27.3%)	0.284
Heart failure history	123 (24.1%)	13 (29.5%)	0.423
Chronic lung disease	99 (19.4%)	12 (27.3%)	0.214
Clinical symptoms and signs at admission			
Dyspnoea	330 (64.7%)	37 (84.1%)	**0.009**
Chest pain	187 (36.7%)	14 (31.8%)	0.521
Syncope	54 (10.6%)	6 (13.6%)	0.532
SBP (mm Hg)	130 (118–149)	111 (100–135)	<**0.001**
Heart rate (bpm)	90 (80–106)	104 (86–115)	**0.008**
Shock index (HR/SBP)	0.7 (0.6–0.8)	0.9 (0.7–1.1)	<**0.001**
Shock index ≥ 1.0	38 (7.5%)	15 (34.1%)	<**0.001**
Respiratory rate (cpm)	20 (16–30)	31 (21−31)	<**0.001**
Temperature (°C)	36.2 (36–36.7)	36.2 (36–36.5)	0.212
SpO_2 (%)	94 (90–97)	91 (88–95)	**0.009**
Altered mental status	63 (12.4%)	9 (20.5%)	0.130
Laboratory data on admission			
Haemoglobin (g/dL)	12.7 (11.3–14)	12.8 (11.7–13.8)	0.632
ALT (U/l)	26 (19–39)	37 (21–97)	**0.003**
Troponin/reference[a]	1.0 (0.5–3.75)	4.1 (1.6–13.6)	**0.003**
Elevated troponin	249 (48.8%)	35 (79.5%)	<**0.001**
NT-proBNP (pg/mL)	916 (240–4075)	4400 (1315–12,176)	<**0.001**
Elevated NT-proBNP	296 (58.0%)	41 (93.2%)	**0.001**
Admission Cr (mg/dL)	0.95 (0.75–1.24)	1.1 (0.8–1.48)	0.323
Baseline Cr (mg/dL)	0.81 (0.70–1.00)	0.80 (0.69–0.98)	0.681
AKI class			**0.016**
None	440 (86.3%)	30 (68.2%)	
I	44 (8.6%)	7 (15.9%)	
II	19 (3.7%)	6 (13.6%)	
III	7 (1.4%)	1 (2.3%)	
MDCT angiography			
Central PE	222 (43.9%)	25 (59.5%)	0.053
RV/LV ratio	0.92 (0.82–1.1)	1.2 (1.0–1.4)	<**0.001**
RV/LV ratio ≥ 1.0	191 (34.5%)	36 (81.8%)	<**0.001**
CV dysfunction[b]	100 (19.6%)	32 (72.7%)	<**0.001**
Arterial blood gas on admission			
FiO_2	0.21 (0.21–0.26)	0.21 (0.21–0.40)	**0.001**
pH	7.45 (7.42–7.47)	7.42 (7.38–7.48)	0.149
$PaCO_2$ (mm Hg)	33 (30–37)	30 (26–37)	0.515
PaO_2 (mm Hg)	70 (60–87)	58 (47–72)	<**0.001**
Lactate (mmol/L)	1.3 (0.9–1.8)	2.9 (1.7–3.6)	<**0.001**
PaO_2/FiO_2	310 (257–371)	210 (157–275)	<**0.001**

Abbreviations: ALT = alanine aminotransferase; AKI = acute kidney injury; Cr = creatinine; CV = cardiovascular; FiO_2 = fraction of inspired oxygen; LV = left ventricle; MDCT = multi-detector computed tomography; NT-proBNP = N-terminal pro b-type natriuretic peptide; $PaCO_2$ and PaO_2 = arterial partial pressure of carbon dioxide and oxygen; PE = pulmonary embolism; RV = right ventricle; SpO_2 = oxygen saturation; SBP = systolic blood pressure.
All continuous values are presented as median (interquartile range). Bold values denote statistical significance.
[a] Since different troponin assays were used, a ratio between measured troponin and reference values was created for statistical analysis. For example, a measured troponin/reference value ratio of 4 would mean that the measured troponin was 4 times higher than the 99th percentile cut-off value.
[b] CV dysfunction was defined as elevated troponin, elevated NT-proBNP and RV/LV ratio ≥ 1.0.

The final model equation is:

$$\text{Probability of event} = [\, \exp(x)/1 + \exp(x)] * 100;$$
where x equals to:
$$1.734 * \mathit{CV\ dysfunction}\ (\mathit{absent} = 0;\ \mathit{present} = 1) +$$
$$1.204 * \mathit{Shock\ index} \geq 1.0\ (\mathit{absent} = 0;\ \mathit{present} = 1) +$$
$$0.321 * \mathit{Lactate}\ (\mathit{absolute\ value\ in\ mmol/L}) -$$
$$0.008 * PaO_2/FiO_2\ (\mathit{absolute\ value}) - 2.383\ (\mathit{constant})$$

The new prediction model for PE-related mortality and/or rescue thrombolysis at 30-days was given the acronym SHIeLD (***S***hock index, ***H***ypoxaem***I***a, ***L***actate and cardiovascular ***D***ysfunction). The SHIeLD score yielded an AUC of 0.90 (95% CI 0.86–0.94; P < 0.001; Supplementary material online) and showed a mild underestimation of risk ($\alpha = 4.7\%$; $\beta = 1.36$; Fig. 1). Internal validation with bootstrapping (1000 samples) yielded an AUC of 0.90 (95% CI 0.85–0.94). The best cut-off (Youden index) was 4.7% with a sensitivity of 91% and a specificity of 77%. The average risk for each tercile was 0.6%, 1.8% and 16.4%, respectively.

Confining our analysis to the secondary endpoints, the AUC of the SHIeLD score was 0.86 (95% CI 0.81–0.90; P < 0.001), 0.81 (95% CI 0.75–0.87; P < 0.001) and 0.87 (95% CI 0.81–0.93; P < 0.001) for all-cause mortality and/or rescue thrombolysis, all-cause mortality and PE-related mortality at 30-days, respectively.

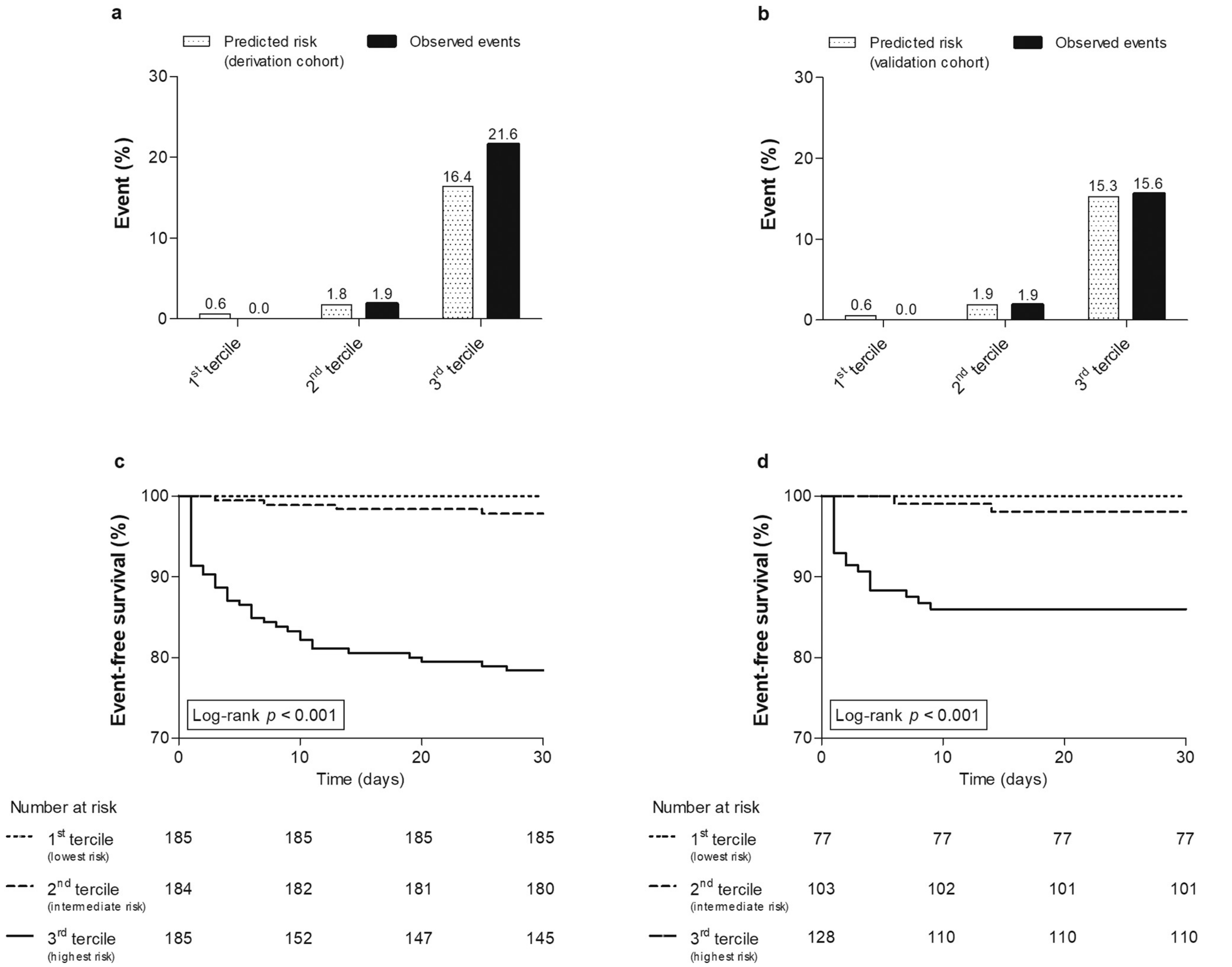

Fig. 1. Calibration plots comparing observed events versus predicted risk by the new score per terciles of risk in the derivation (a) and external validation (b) cohorts. Kaplan-Meier estimated event-free survival rates per risk strata in the derivation (c) and external validation (d) cohorts. Event refers to PE-related mortality and/or rescue thrombolysis at 30-days.

A web-based application to calculate the risk based on our model is available at http://www.ebimed.pt/SHIeLD_score.php.

3.3. External validation

The external validation was conducted on 308 patients (20 events). The SHIeLD score achieved an AUC of 0.82 (95% CI 0.75–0.89; P < 0.001; Supplementary material online). Calibration analysis showed a slight underestimation of risk in this cohort ($\alpha = -0.3\%$; $\beta = 1.05$; Fig. 1). The best risk cut-off (Youden index) was 4.2%, with a sensitivity of 90% and a specificity of 67%. The average risk for each tercile was 0.6%, 1.9% and 15.3%, respectively.

Confining our analysis to the secondary endpoints, the AUC of the SHIeLD score was 0.81 (95% CI 0.75–0.87; P < 0.001), 0.78 (95% CI 0.71–0.85; P < 0.001) and 0.79 (95% CI 0.70–0.88; P < 0.001) for all-cause mortality and/or rescue thrombolysis, all-cause mortality and PE-related mortality at 30-days, respectively.

The incidence of the study's primary endpoint was statistically similar across the predefined risk terciles in both the derivation and external validation cohorts, which also corroborates a good calibration: 0.0% vs 0.0% (1st tercile, lowest risk); 2.2% vs 1.9% (2nd tercile, intermediate risk; P = 0.897) and; 21.6% vs. 14.3% (3rd tercile, highest risk; P = 0.09). Kaplan-Meier analysis showed a statistically significant survival difference between the three predefined risk strata (Fig. 1).

3.4. Clinical utility of the SHIeLD model

To evaluate the clinical utility of the SHIeLD score, a decision curve analysis was used (Fig. 2). The new score displayed consistent positive and larger net benefit across a broad range of risk thresholds compared

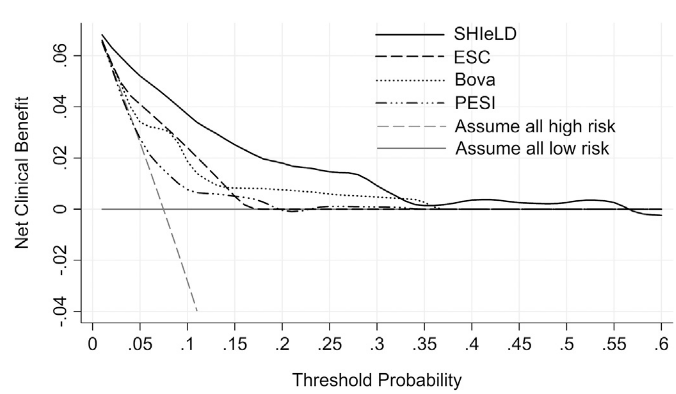

Fig. 2. Decision curve analysis – net benefit of using the SHIeLD score to predict PE-related mortality and/or rescue thrombolysis at 30-days as compared with the ESC, PESI and Bova models for different risk thresholds. ESC, European Society of Cardiology; PE, pulmonary embolism; PESI, PE severity index.

to the ESC, PESI and Bova models. For example, at a decision threshold of 10% risk of PE-related mortality and/or thrombolysis at 30-days, the SHIeLD score would identify 2 additional true events per 100 patients without increasing the number of false positive predictions when compared with the ESC model. Likewise, it would identify 3 additional true events per 100 patients when compared with the PESI score. If we consider a 20% probability of PE-related death or need for rescue thrombolysis as the acceptable cut-off for treatment decision, the SHIeLD score would have a sensitivity of 45%, specificity of 94% and positive predictive value of 37%, while retaining a negative predictive value of 96% (see Supplementary material online).

Also, the discriminative ability of our model was superior to that of the ESC, Bova and PESI scores (see Supplementary material online).

3.5. Sensitivity analysis

Results remained similar after exclusion of patients with missing values (see Supplementary material online).

4. Discussion

After an initial episode of acute PE, normal blood pressure can be maintained by compensatory inotropic and chronotropic stimulation and peripheral vasoconstriction. Even though the prognosis of patients with normotensive PE is generally good, a small but significant proportion (around 8%) will have a complicated course which might be explained by a vicious cycle of ongoing RV ischemia and dysfunction that may ultimately overcome these compensatory mechanisms [4,14–16]. Identifying these patients at risk on admission is a challenging task. At present, European guidelines recommend risk stratification of normotensive PE in three strata according to the PESI score and the presence of imaging and biochemical markers of RV dysfunction [1]. While the ESC model performs excellently in identifying low-risk patients, there is evidence to suggest that the prognosis of intermediate-risk patients is sufficiently heterogeneous to warrant refinements in risk stratification [2,3,17–19]. We hypothesized that identifying signs of systemic distress that usually precede overt hypotension might improve the prognostic assessment of normotensive PE patients. Serum lactate, shock index and the PaO_2/FiO_2 ratio were thus selected as possible adjuncts to risk stratification based on validated prognostic value and easy accessibility in the emergency department [20–24]. We developed and validated a new score that adds this set of variables to established markers of RV injury already present in the current decision criteria [6,9,25–29]. Three important aspects of a risk prediction model were assessed: discrimination, calibration and clinical utility (decision curve analysis). The SHIeLD score (***S***hock index, ***H***ypoxaem***I***a, ***L***actate and cardiovascular ***D***ysfunction) showed good discriminative power, substantiated by a C-statistic of 0.90 and 0.82 in the derivation and external validation cohorts, respectively. Model calibration was also good, with a calibration slope of 1.05 in the external validation cohort supporting the accuracy of the score. Finally, the SHIeLD score seems to recognize a higher proportion of true positive cases than the recommended ESC model as well as the Bova score, highlighting its potential clinical usefulness.

Several scores have been developed for the prediction of a complicated course in normotensive PE. The score by Bova et al. includes a grading system with RV dysfunction, myocardial injury, systolic blood pressure, and heart rate to predict PE-related mortality, haemodynamic decompensation and recurrent PE at 30-days [4]. The eStiMaTe score combines the simplified PESI with troponin, BNP and lower limb ultrasound to identify normotensive PE patients at risk of all-cause mortality, haemodynamic collapse and recurrent PE at 30-days [5]. Despite minor differences in primary outcomes, both scores were shown to have a discriminative ability similar to the SHIeLD score in external validation cohorts (eStiMaTe 0.85, Bova 0.80) [5,30]. One important drawback of these scores is the need to perform echocardiography and/or lower limb ultrasound. These tests may not be readily available on admission or even within the first 24 h, which is the timeframe when most events occur. Unlike the aforementioned risk stratification strategies, the SHIeLD score can stratify patients almost immediately after diagnosis, as it includes variables routinely searched for in patients presenting with suspected PE. Still, the recently modified FAST score that combines tachycardia, syncope and high-sensitivity troponin, can also be rapidly applied after PE diagnosis [30]. Unfortunately, a direct comparison between the modified FAST score and the SHIeLD model was not possible since the vast majority of our patients only had conventional troponin measured.

Although there is a continuum of risk, prognostic assessment must be translated into a dichotomous decision of whether to conduct reperfusion therapies. Moreover, there is no consensus on which risk threshold justifies the use of a more aggressive therapy in this population, and this will probably depend on the clinical setting and patients' characteristics. To assist in making this decision, we performed the decision curve analysis, a method for evaluating the net benefit of a diagnostic test across a range of perceived risks. If a >20% probability of PE-related death or need for rescue thrombolysis is accepted as the threshold for treatment decision [31], the SHIeLD score would have a sensitivity of 45%, specificity of 94% and positive predictive value of 37%, while retaining a negative predictive value of 96%. Although we have categorized our population into 3 risk strata, one should bear in mind that our highest risk subgroup does not necessarily correspond to the best cut-off for intervention. Users of the SHIeLD score might choose to employ other clinically meaningful risk thresholds.

5. Limitations

Several limitations of this study should be acknowledged. This was a retrospective analysis of normotensive PE patients with a relatively long recruitment period during which there was an update in European PE guidelines. Yet, it is very unlikely that results were compromised since similar management strategies were recommended for 'high-risk' and 'non-high-risk' PE patients in both 2008 and 2014 ESC guidelines [1,32]. On the other hand, it should also be mentioned that there is a relatively small number of events, especially in the validation cohort. Our study focused on the prediction of death or need for urgent thrombolysis and morbidity amongst survivors was not assessed. In order to deal with missing data, we had to employ multiple imputation techniques. However, significant bias seems unlikely since sensitivity analysis (excluding patients with missing data) yielded similar results. Even though the selected variables are readily obtainable on admission, the SHIeLD score cannot be easily calculated by hand. Since prediction tools are useful only when they are accessible at the point of care, we built an online calculator to assist in that process. While we have not considered echocardiography data to define RV dysfunction it is reasonable to assume that RV dysfunction can also be defined by this method. Indeed, results remained similar in a supplementary analysis where available echocardiography data at presentation in the emergency department was also used. Some centres may not have access to NT-proBNP but the cut-off and prognostic value of BNP is also published in the setting of PE, therefore it is reasonable to use it as an alternative to NT-proBNP. Although we performed external validation, the portability of this score to other populations needs to be confirmed given the lack of appropriate power in the validation cohort (few events). However, it is worth mentioning that events are relatively rare in the subgroup of normotensive PE. Finally, our score was devised to estimate the risk of adverse outcome and aid decision-making, but it is no substitute for sound clinical judgment.

6. Conclusions

A risk score to predict 30-days PE-related mortality and/or rescue thrombolysis in patients with normotensive PE was developed from variables that are readily available on admission and was validated in an external population. The SHIeLD score (***S***hock index, ***H***ypoxaem***I***a, ***L***actate and cardiovascular ***D***ysfunction) showed good discrimination and calibration and seems to outperform the current recommended decision criteria. If validated in other datasets, this score might prove to be a useful tool to assist physicians in selecting patients for closer monitoring or a more aggressive treatment strategy.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

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